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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/551,449	09/29/2005	Tatsuhiko Kodama	278547US0X PCT	2982

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EXAMINER	
MAKAR, KIMBERLY A	
ART UNIT	**PAPER NUMBER**
1636	

NOTIFICATION DATE	DELIVERY MODE
01/29/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/551,449	KODAMA ET AL.	
	Examiner	Art Unit	
	Kimberly A. Makar, Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 October 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17-20 and 22-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-20, 22-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *05/09/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendments to claims in their response filed 10/05/07 are acknowledged. Applicants have cancelled claims 1-16 and 21. Applicants have amended claim 170. Applicants have further added new claims 25-33.

Priority

2. In the previous office action, priority of the claims was given the date of filing of the instant specification, as the provisional application was filed in Japanese, and no English translation was provided.

3. Applicants have provided an English translation that has been certified in their response dated 06/26/07.

4. Thus priority to the instant claims 17-20 and 22-33 are given the priority date of 04/17/03.

5. In the previous office action the following rejections were made:

- Claims 1-5 were rejected under an obvious type double patenting rejection over Patent 5,011,930. ***This rejection is withdrawn in light of applicant's cancellation of claims 1-5.***
- Claims 1-5 were rejected under an obvious type double patenting rejection over Patent 5,284,953. ***This rejection is withdrawn in light of applicant's cancellation of claims 1-5.***

- Claims 1-5 were rejected under an obvious type double patenting rejection over 5,854,259. ***This rejection is withdrawn in light of applicant's cancellation of claims 1-5.***
- Claims 1-5, 9-13, 17-21 were rejected under an obvious type double patenting rejection over Patent 5,856,336.
- Claims 1-5, 9-13, 17-21 were rejected under an obvious type double patenting rejection over Patent 5,872,130.
- Claims 1-5 were rejected under an obvious type double patenting rejection over Patent 6,465,477. ***This rejection is withdrawn in light of applicant's cancellation of claims 1-5.***
- Claims 9-13, 17-21 were rejected under an obvious type double patenting rejection over Patent 7,022,713.
- Claims 1-5 were provisionally rejected under an obvious type double patenting rejection over Patent Application Publication US2004/0018235. ***This rejection is withdrawn in light of applicant's cancellation of claims 1-5.***
- Claims 9-13, 17-21 were provisionally rejected under an obvious type double patenting rejection over Patent Application Publication US2003/0195167. ***This rejection is withdrawn in light of the abandonment of US2003/0195167.***
- Claims 1-5, 9-13, 17-21 were provisionally rejected under an obvious type double patenting rejection over Patent Application Publication US2005/0148626.

- Claims 1-5 were provisionally rejected under an obvious type double patenting rejection over Patent Application Publication US2006/0111437. ***This rejection is withdrawn in light of applicant's cancellation of claims 1-5.***
- Claims 9-13, 17-21 were provisionally rejected under an obvious type double patenting rejection over Patent Application Publication US2006/0217352.
- Claims 1-5, 9-13, 17-21 were provisionally rejected under an obvious type double patenting rejection over Patent Application Publication US2006/0257474.
- Claims 2, 9,18 were rejected under 112 2nd paragraph as being indefinite.
- Claims 1-5 were rejected under 35 U.S.C. 102(b/e) as being anticipated by Fujikawa et al (US Patent No. 5,011,930). ***This rejection is withdrawn in light of applicant's cancellation of claims 1-5.***
- Claims 1-5 were rejected under 35 U.S.C. 102(b/e) as being anticipated by Ohara et al (US Patent No. 5,284,953). ***This rejection is withdrawn in light of applicant's cancellation of claims 1-5.***
- Claims 1-5 were rejected under 35 U.S.C. 102(b/e) as being anticipated by Fujikawa et al (US Patent No. 5,854,259). ***This rejection is withdrawn in light of applicant's cancellation of claims 1-5.***
- Claims 1-5, 9-13, 17-21 were rejected under 35 U.S.C. 102(b/e) as being anticipated by Fujikawa et al (US Patent No. 5,856,336).
- Claims 1-5 were rejected under 35 U.S.C. 102(b/e) as being anticipated by Muramatsu et al (US Patent No. 6,465,477). ***This rejection is withdrawn in light of applicant's cancellation of claims 1-5.***

- Claims 9-13, 17-21 were rejected under 35 U.S.C. 102(b/e) as being anticipated by Aoki et al (US Patent No. 7,022,713). ***This rejection is withdrawn in light of applicant's priority date of 04/17/03, as Akoi et al is no longer applicable under 102 or 103.***
- Claims 9-13,17-21 were rejected under 35 U.S.C. 102(b/e) as being anticipated by Morikawa et al (US Patent Publication No. US 2003/0195167).
- Claims 1-5 were rejected under 35 U.S.C. 102(b/e) as being anticipated by Tanizawa et al (US Patent Publication No. US 2004/0018235) published 01/29/04. ***This rejection is withdrawn in light of applicant's cancellation of claims 1-5.***
- Claims 1-5, 9-13, and 17-21 were rejected under 35 U.S.C. 102(e) as being anticipated by Oida et al (US Patent Publication No US 2005/0148626) published 07/07/2005. ***This rejection is withdrawn in light of applicant's priority date of 04/17/03, as Oida et al is no longer applicable under 102 or 103.***
- Claims 1-5 were rejected under 35 U.S.C. 102(e) as being anticipated by Aoki et al (US Patent Publication No US 2006/0111437) published 05/25/2006. ***This rejection is withdrawn in light of applicant's cancellation of claims 1-5.***
- Claims 9-13, 17-21 were rejected under 35 U.S.C. 102(e) as being anticipated by Yokoyanna et al (US Patent Publication No US 2006/0217352) published 07/28/2006. ***This rejection is withdrawn in light of applicant's priority date of 04/17/03, as Yokoyanna et al is no longer applicable under 102 or 103.***

- Claims 1-5, 9-13, 17-21 were rejected under 35 U.S.C. 102(e) as being anticipated by Nakagawa et al (US Patent Publication No US 2006/025747) published 11/16/2006. ***This rejection is withdrawn in light of applicant's priority date of 04/17/03, as Nakagawa et al is no longer applicable under 102 or 103.***
- Claims 1-4, 6-7, 9-12, 14-15, 17-20 and 22-23 were rejected under 102(a) as being anticipated by Parmer et al. ***This rejection is withdrawn in light of applicant's priority date of 04/17/03, as Parmer et al is no longer applicable under 102 or 103.***
- Claims 1-4, 8-12, 16-20, 24 were rejected as being anticipated by Hausding et al.
- Claims 1, 6-7, 9, 14-15, 17, 22, and 23 were rejected under 102(b) as being anticipated by Lerner et al.
- Claims 5, 13, and 21 were rejected under 103(a) as being obvious over Parmer et al in view of Maejima et al. ***This rejection is withdrawn in light of applicant's priority date of 04/17/03, as Parmer et al is no longer applicable under 102 or 103.***
- Claims 8,16, and 24 were rejected under 103(a) as being obvious over Parmer et al in view of Hausding et al. ***This rejection is withdrawn in light of applicant's priority date of 04/17/03, as Parmer et al is no longer applicable under 102 or 103***.

6. The following rejections are necessitated by applicant's amendments dated 10/05/07. Applicants have amended their claims to read on a method of treating a

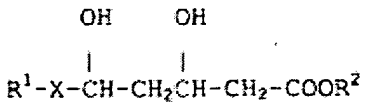
subject in need there of suffering from a blood vessel disorder. Such limitations were not found in previous claim sets.

Election/Restrictions

7. Applicant's election of a cerebral hemorrhage in the reply filed on 10/05/07 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

For the purposes of prosecution the following is defined:

8. Page 4 of the specification teaches the formula (1):



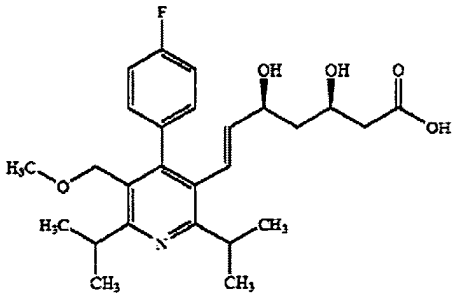
Page 9 of specification further teaches:

9. Compounds represented by the formula (1), their lactone derivatives and salts of these compounds and lactone derivatives, all of which are usable in the present invention, are known as HMG-COA reductase inhibitors useful as hyperlipidemia therapeutics.

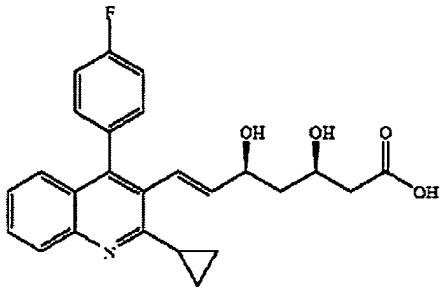
10. Thus for the purposes of prosecution, any HMG-CoA reductase inhibitor comprises the basic formula (1) as defined by applicant.

11. Storz (U.S. Patent No. 6,909,003) teaches the chemical structures of several well known statins:

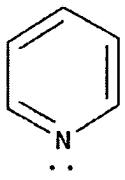
Cerivastatin



Pitavasatin



12. both structures have, at the very least a pyridyl group:



Pyridine. Milton Orchin. The Vocabulary and Concepts of Organic Chemistry *2Nd Ed.* Hoboken, N.J John Wiley & Sons, Inc. (US), 2005. pg 78.

Double Patenting

13. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir.

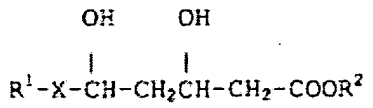
1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

14. A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

15. Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

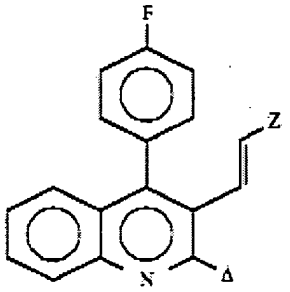
16. The following rejections are modified to address applicant's amendments dated 10/15/07.

17. Claims 17-21, 25-28 and 33 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 2 of U.S. Patent No. 5,856,336 in view of Gertz et al (Withdrawal of Statin Treatment Abrogates Stroke Protection in Mice, Stroke, 2003. 34:551-557). Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 17-21, 25-28 and 33 of the instant application represent a genus over the species claim 2 in U.S. Patent No. 5,856,336. Instant claims 17-21, 25-28 and 33 read on a method for promoting expression of LKLF/KLF2 gene, which comprises administering to a subject in need thereof a mevalonic acid metabolic pathway inhibitor, wherein the subject suffers from a disease associated with a blood vessel disorder, with the proviso that the blood vessel disorder is not atherosclerosis, wherein the compound capable of inhibiting a mevalonic pathway, wherein the compound is represented by the formula (1):



wherein the compound comprises a variety of cyclic R groups and is limited to the lovastatin, pravastatin, simvastatin, fluvastatin cerivastatin, atorvastatin, rosuvastatin, mevastatin, or pitavastin and the blood vessel disorder is cerebral hemorrhage. Broadly, these claims read on a method of inherently increasing LKLF expression by the administration of a mevalonic acid pathway inhibitor, including well known statins, to any subject in need thereof, with the proviso that the blood disorder is not atherosclerosis.

18. Patent 5,856,336 discloses the chemical structure for pitavastatin in claim 1:



19. Z—CH(OH)—CH_2—CH(OH)—CH_2—COO.½Ca. , and the methods for the use of pitavastatin in claim 2, specifically, "A method for reducing hyperlipidemia, hyperlipoproteinemia or atherosclerosis, which comprises administering an effective amount of the compound of formula A as defined in claim 1". The structure of the molecule of patent 5,856,336 inherently embodies the structural limitations of the instant method claims. However, Patent 5,856,336 is limited to treating atherosclerosis, or hyperlipidemia or hyperlipoproteinemia", not a blood vessel disorder, including cerebral hemorrhage.

20. The instant specification does not define "a disease associated with a blood vessel disorder" nor "cerebral hemorrhage."

21. The Colombia Encyclopedia, 2004 teaches the definition of stroke:

22. Destruction of brain tissue as a result of intracerebral hemorrhage or infarction caused by thrombosis (clotting) or embolus (obstruction in a blood vessel caused by clotted blood or other foreign matter circulating in the bloodstream); formerly called apoplexy. Cerebral hemorrhage or thrombosis occurs most often in elderly persons with constricted arteries (see arteriosclerosis), although either may also be caused by inflammatory or toxic damage to the cerebral blood vessels. Cerebral embolism may occur at any age, even in children.
23. Symptoms of stroke develop suddenly. In cases of severe brain damage there may be deep coma, paralysis of one side of the body, and loss of speech, followed by death or permanent neurological disturbances after recovery. If the brain damage sustained has been slight, there is usually complete recovery, but most survivors of stroke require extensive rehabilitation. Hypertension, which is a major cause of intracranial hemorrhage and stroke, can be treated by preventive measures using diet (e.g., increasing nutrients such as antioxidants and folate), drug therapy, and stress reduction techniques. Other preventive measures for people at high risk include daily aspirin to retard clot formation and surgical correction of the narrowed carotid artery. Sometimes surgical removal of the clot is possible on larger vessels, but it is usually pointless after the stroke or when blockage is widespread. The thrombolytic drug tissue plasminogen activator, widely used to treat heart attacks, has been approved for use within three hours of the onset of strokes caused by clots.

24. Using the broadest reasonable interpretation, "stroke" and "thrombosis" and "cerebral hemorrhage" read on "a disease that is associated with "a blood vessel disorder, with the proviso that the blood disorder is not atherosclerosis."

25. Gertz et al (Withdrawal of Statin Treatment Abrogates Stroke Protection in Mice, Stroke, 2003. 34:551-557) teaches that the use of statins, including atorvastatin provides neuronal protection and reduces thrombus formation in mice, independent of lipid lowering in mice (see abstract). Gertz teaches that statins have many pleiotropic effects, other than mevalonic acid pathway inhibitors, including reducing myocardial infarct size and stroke possibly through direct effects on endothelium with antithrombotic

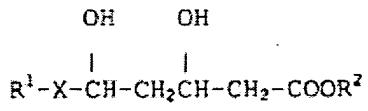
and anti-inflammatory effects, that statins have been shown to upregulate eNOS in vasculature and thrombocytes, decrease platelet activation, augment cerebral blood flow, and protect from cerebral ischemia in wild-type mice (see page 551).

26. The administration of a statin would inherently cause an increase in expression of LKLF/KLF2. Furthermore, there is no teaching in the specification of how the mevalonic acid metabolic pathway inhibitors are different that those used in the prior art. In fact, in the examples 1-3 of the specification, applicant merely teaches the incubation of HUVEC cells with known mevalonic acid inhibitors and measures KLF2 expression. The known inhibitors, known well before the date of filing of the instant application, inherently have the capability of increasing KLF2 expression.

27. It would have been obvious to the skilled artisan to combine the teachings of Patent No. 5,856,336 on a method of administering a well known statin for treating atherosclerosis, hyperlipidemia or hyperlipoproteinemia, with the teaching of Gertz et al on the many pleiotropic effects of statins make them good candidates for treating other diseases, including those associated with blood vessel disorders, including thrombosis, cerebral hemorrhage and stroke. Since the instant methodology relies upon the inherent effects of a known compound, and the use of the compound to treat other disease was known in the art, a skilled artisan would have a reasonable degree of success in practicing the claimed invention. All of the claimed elements were known in the prior art, and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would

have yielded predictable result to one of ordinary skill in the art at the time of the invention ((*See KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007)).

28. Claims 17-21, 25-28 and 33 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 5 of U.S. Patent No. 5,872,130 in view of Gertz et al (Withdrawal of statin Treatment Abrogates Stroke Protection in Mice, Stoke, 2003. 34:551-557). Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 17-21, 25-28 and 33 of the instant application represent a genus over the species claim 5 in U.S. Patent No. 5,872,130. Instant claims 17-21, 25-28 and 33 read on a method for promoting expression of LKLF/KLF2 gene, which comprises administering to a subject in need thereof a mevalonic acid metabolic pathway inhibitor, wherein the subject suffers from a disease associated with a blood vessel disorder, with the proviso that the blood disorder is not atherosclerosis, wherein the compound capable of inhibiting a mevalonic pathway, wherein the compound is represented by the formula (1):



wherein the compound comprises a variety of cyclic R groups and is limited to the lovastatin, pravastatin, simvastatin, fluvastatin, cerivastatin, atorvastatin, rosuvastatin, mevastatin, or pitavastin and the blood vessel disorder is cerebral hemorrhage. Broadly, these claims read on a method of inherently increasing LKLF expression by the administration of a mevalonic acid pathway inhibitor, including well known statins, to any

subject in need thereof suffering from a blood disorder, with the proviso that the blood disorder is not atherosclerosis.

29. Claim 5 of US Patent No. 5,872,130 comprise methods of using HMG-CoA reductase inhibitors, and include embodiments including pitavastatin. Claim 5 of 5,872,130 recites, "A method for reducing hyperlipidemia, hyperlipoproteinemia or atherosclerosis, which comprises administering an effective amount of the compound of formula A as defined in claim 1." However, Claim 5 is limited to treating atherosclerosis, or hyperlipidemia or hyperlipoproteinemia, not a blood vessel disorder, including cerebral hemorrhage.

30. The instant specification does not define "a disease associated with a blood vessel disorder" nor "cerebral hemorrhage."

31. Using the broadest reasonable interpretation, "stroke" and "thrombosis" and "cerebral hemorrhage" read on "a disease that is associated with "a blood vessel disorder, with the proviso that the blood disorder is not atherosclerosis." (see above).

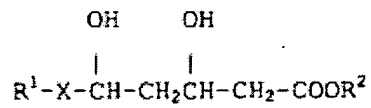
32. Gertz et al (Withdrawal of statin Treatment Abrogates Stroke Protection in Mice, Stroke, 2003. 34:551-557) teaches that the use of statins, including atorvastatin provides neuronal protection and reduces thrombus formation in mice, independent of lipid lowering in mice (see abstract) Gertz teaches that statins have many pleiotropic effects, other than mevalonic acid pathway inhibitors, including, reducing myocardial infarct size and stroke possibly through direct effects on endothelium with antithrombotic and anti-inflammatory effects, that statins have been shown to upregulate eNOS in

vasculature and thrombocytes, decrease platelet activation, augment cerebral blood flow, and protect from cerebral ischemia in wild-type mice (see page 551).

33. The administration of a statin would inherently cause an increase in expression of LKLF/KLF2. Furthermore, there is no teaching in the specification of how the mevalonic acid metabolic pathway inhibitors are different that those used in the prior art. In fact, in the examples 1-3 of the specification, applicant merely teaches the incubation of HUVEC cells with known mevalonic acid inhibitors and measures KLF2 expression. The known inhibitors, known well before the date of filing of the instant application, inherently have the capability of increasing KLF2 expression.

34. It would have been obvious to the skilled artisan to combine the teachings of Patent No. 5,872,130 on a method of administering a well known statin for treating atherosclerosis, hyperlipidemia or hyperlipoproteinemia, with the teaching of Gertz et al on the many pleiotropic effects of statins that make statins good candidates for treating other diseases, including those associated with blood disorder, including thrombosis, cerebral hemorrhage and stroke. Since the instant methodology relies upon the inherent effects of known compound, and the use of the compound to treat other diseases was known in the art, a skilled artisan would have a reasonable degree of success in practicing the claimed invention. All of the claimed elements were known in the prior art, and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable result to one of ordinary skill in the art at the time of the invention ((*See KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007)).

35. Claims 17-21, 25-28 and 33 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-2 of U.S. Patent No. 7,022,713 in view of Gertz et al (Withdrawal of Statin Treatment Abrogates Stroke Protection in Mice, Stoke, 2003. 34:551-557). Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 17-21, 25-28 and 33 of the instant application represent a genus over the species claims 1-2 in U.S. Patent No. 7,022,713. Instant claims 17-21, 25-28 and 33 read on a method for promoting expression of LKLF/KLF2 gene, which comprises administering to a subject in need thereof a mevalonic acid metabolic pathway inhibitor, wherein the subject suffers from a disease associated with a blood vessel disorder, with the proviso that the blood disorder is not atherosclerosis, wherein the compound capable of inhibiting a mevalonic pathway, wherein the compound is represented by the formula (1):



wherein the compound comprises a variety of cyclic R groups and is limited to the lovastatin, pravastatin, simvastatin, fluvastatin, cerivastatin, atorvastatin, rosuvastatin, mevastatin, or pitavastin and the blood vessel disorder is cerebral hemorrhage. Broadly, these claims read on a method of inherently increasing LKLF expression by the administration of a mevalonic acid pathway inhibitor, including well known statins, to any subject in need thereof suffering from a blood disorder, with the proviso that the blood disorder is not atherosclerosis.

36. Claims 1-2 of U.S. Patent No. 7,022,713 recite "a method for treating hypertriglyceridemia in a patient in need of such treatment comprising administering a synergistically effective blood-triglyceride decreasing amount of a combination of a pitavastatin and eicosapentaenoic acid or an ester thereof" and "a method according to claim 1, wherein the pitavastin is pitavastin calcium and the eicosapentaenoic acid or ester thereof is ethyl eicosapentaenoate" respectively. The administration of the pharmaceutical compositions comprising HMG-CoA reductase inhibitors including pitavastatin would inherently cause an increase in expression of LKLF/KLF2. Furthermore, there is no teaching in the specification of how the mevalonic acid metabolic pathway inhibitors of the instant application are different than those used in the prior art. In fact, in the examples 1-3 of the specification, applicant merely teaches the incubation of HUVEC cells with known mevalonic acid inhibitors and measures KLF2 expression. The known inhibitors, known well before the date of filing of the instant application, inherently have the capability of increasing KLF2 expression.

37. However, claims 1 and 2 of patent 7,022,713 do not read on a blood vessel disorder including cerebral hemorrhage.

38. The instant specification does not define "a disease associated with a blood vessel disorder" nor "cerebral hemorrhage."

39. Using the broadest reasonable interpretation, "stroke" and "thrombosis" and "cerebral hemorrhage" read on "a disease that is associated with "a blood vessel disorder, with the proviso that the blood disorder is not atherosclerosis." (see above rejection).

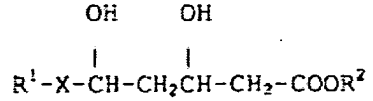
40. Gertz et al (Withdrawal of Statin Treatment Abrogates Stroke Protection in Mice, Stroke, 2003. 34:551-557) teaches that the use of statins, including atorvastatin provides neuronal protection and reduces thrombus formation in mice, independent of lipid lowering in mice (see abstract) Gertz teaches that statins have many pleiotropic effects, other than mevalonic acid pathway inhibitors, including, reducing myocardial infarct size and stroke possibly through direct effects on endothelium with antithrombotic and anti-inflammatory effects, that statins have been shown to upregulate eNOS in vasculature and thrombocytes, decrease platelet activation, augment cerebral blood flow, and protect from cerebral ischemia in wild-type mice (see page 551).

41. The administration of a statin would inherently cause an increase in expression of LKLF/KLF2. Furthermore, there is no teaching in the specification of how the mevalonic acid metabolic pathway inhibitors are different that those used in the prior art. In fact, in the examples 1-3 of the specification, applicant merely teaches the incubation of HUVEC cells with known mevalonic acid inhibitors and measures KLF2 expression. The known inhibitors, known well before the date of filing of the instant application, inherently have the capability of increasing KLF2 expression.

42. It would have been obvious to the skilled artisan to combine the teachings of Patent No. 7,022,713 on a method of administering a well known statin for treating hypertriglyceridemia, with the teaching of Gertz et al on the many pleiotropic effects of statins that make statins good candidates for treating other diseases, including those associated with blood vessel disorders, including thrombosis, cerebral hemorrhage and stroke. Since the instant methodology relies upon the inherent effects of known

compound, and the use of the compound to treat other diseases was known in the art, a skilled artisan would have a reasonable degree of success in practicing the claimed invention. All of the claimed elements were known in the prior art, and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention ((*See KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007)).

43. Claims 17-21, 25-28 and 33 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 7-13 of U.S. Patent Publication No. US 2005/0148626 in view of Houston et al (Tissue factor- a therapeutic target for thrombotic disorders, Expert Opinion in Therapeutic Targets, 2002. 6(2):159-174). Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 17-21, 25-28 and 33 of the instant application represent a genus over the species claims 7-13 in U.S. Patent Publication No. US 2005/0148626. Instant claims 17-21, 25-28 and 33 read on a method for promoting expression of LKLF/KLF2 gene, which comprises administering to a subject in need thereof a mevalonic acid metabolic pathway inhibitor, wherein the subject suffers from a disease associated with a blood vessel disorder, with the proviso that the blood disorder is not atherosclerosis, wherein the compound capable of inhibiting a mevalonic pathway, wherein the compound is represented by the formula (1):



wherein the compound comprises a variety of cyclic R groups and is limited to the lovastatin, pravastatin, simvastatin, fluvastatin cerivastatin, atorvastatin, rosuvastatin, mevastatin, or pitavastin and the blood vessel disorder is cerebral hemorrhage. Broadly, these claims read on a method of inherently increasing LKLF expression by the administration of a mevalonic acid pathway inhibitor, including well known statins, to any subject in need thereof suffering from a blood disorder, with the proviso that the blood disorder is not atherosclerosis.

44. Claims 7-13 of U.S. Patent Publication No. US 2005/0148626 comprise a thrombomodulin expression promoter comprising the HMG-CoA reductase inhibitor pitavastatin and methods of treating a patient with sepsis and/or a coagulation disorder with the compound. The administration of the HMG-CoA reductase inhibitors including pitavastatin and atorvastatin would inherently cause an increase in expression of LKLF/KLF2. Furthermore, there is no teaching in the specification of how the mevalonic acid metabolic pathway inhibitors of the instant application are different than those used in the prior art. In fact, in the examples 1-3 of the specification, applicant merely teaches the incubation of HUVEC cells with known mevalonic acid inhibitors and measures KLF2 expression. The known inhibitors, known well before the date of filing of the instant application, inherently have the capability of increasing KLF2 expression.

45. However, claims 7-13 of U.S. Patent Publication No. US 2005/0148626 do not read on a blood vessel disorder including cerebral hemorrhage.

46. The instant specification does not define "a disease associated with a blood vessel disorder" nor "cerebral hemorrhage."

47. Using the broadest reasonable interpretation, "stroke" and "thrombosis" and "cerebral hemorrhage" read on "a disease that is associated with "a blood vessel disorder, with the proviso that the blood disorder is not atherosclerosis." (see above rejection).

48. Houston et al (Tissue factor- a therapeutic target for thrombotic disorders, Expert Opinion in Therapeutic Targets, 2002. 6(2):159-174) teaches that thrombosis is the main cause of most cases of myocardial infarction and stroke (see page 159). Houston reviews the role of tissue factor in the development of both thrombosis and atherosclerosis, and ways to inhibit tissue factor to reduce the coagulation effects of TF (see pages 160-162). Houston teaches that statins have been shown to inhibit TF expression, and that the pleiotropic effects of statins are known to induce alterations in the coagulation pathway (page 163-165, table 1).

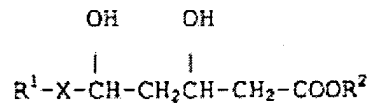
49. The administration of a statin would inherently cause an increase in expression of LKLF/KLF2. Furthermore, there is no teaching in the specification of how the mevalonic acid metabolic pathway inhibitors are different that those used in the prior art. In fact, in the examples 1-3 of the specification, applicant merely teaches the incubation of HUVEC cells with known mevalonic acid inhibitors and measures KLF2 expression. The known inhibitors, known well before the date of filing of the instant application, inherently have the capability of increasing KLF2 expression.

50. It would have been obvious to the skilled artisan to combine the teachings of Patent application US 2005/0148626 on a method of administering a well known statin

for treating a coagulation disorder, with the teaching of Houston et al on the leading cause of stroke is via thrombosis and the many beneficial effects of statins make them good candidates for anticoagulants, including those associated with blood disorder, including thrombosis, and stroke. Since the instant methodology relies upon the inherent effects of known compound, and the use of the compound to treat other diseases was known in the art, and thrombosis is associated with stroke and cerebral hemorrhage, a skilled artisan would have a reasonable degree of success in practicing the claimed invention. All of the claimed elements were known in the prior art, and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention ((*See KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007)). *This is a provisional double patenting rejection.*

51. Claims 17-21, 25-28 and 33 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-17 of U.S. Patent Publication No. US 2006/0217352 in view of Houston et al (Tissue factor- a therapeutic target for thrombotic disorders, Expert Opinion in Therapeutic Targets, 2002. 6(2):159-174). Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 17-21, 25-28 and 33 of the instant application represent a genus over the species claims 1-17 in U.S. Patent Publication No. US 2006/0217352. Claims 17-21, 25-28 and 33 read on a method for promoting

expression of LKLF/KLF2, which comprises administering to a subject in need thereof a mevalonic acid metabolic pathway inhibitor, wherein the subject suffers from a disease associated with a blood vessel disorder, with the proviso that the blood disorder is not atherosclerosis, wherein the compound capable of inhibiting a mevalonic pathway, wherein the compound is represented by the formula (1):



wherein the compound comprises a variety of cyclic R groups and is limited to the lovastatin, pravastatin, simvastatin, fluvastatin, cerivastatin, atorvastatin, rosuvastatin, mevastatin, or pitavastin and the blood vessel disorder is cerebral hemorrhage. Broadly, these claims read on a method of inherently increasing LKLF expression by the administration of a mevalonic acid pathway inhibitor, including well known statins, to any subject in need thereof suffering from a blood disorder, with the proviso that the blood disorder is not atherosclerosis.

52. Claims 1-17 of U.S. Patent Publication No. US 2006/0217352 comprise a method for treating thrombosis by the administration of effective doses of pitavastatin. The administration of the HMG-CoA reductase inhibitor pitavastatin would inherently cause an increase in expression of LKLF/KLF2. Furthermore, there is no teaching in the specification of how the mevalonic acid metabolic pathway inhibitors of the instant application are different than those used in the prior art. In fact, in the examples 1-3 of the specification, applicant merely teaches the incubation of HUVEC cells with known

mevalonic acid inhibitors and measures KLF2 expression. The known inhibitors, known well before the date of filing of the instant application, inherently have the capability of increasing KLF2 expression.

53. However, claims 1-17 of U.S. Patent Publication No. US 2006/0217352 do not read on a blood vessel disorder including cerebral hemorrhage.

54. The instant specification does not define "a disease associated with a blood vessel disorder" nor "cerebral hemorrhage."

55. Using the broadest reasonable interpretation, "stroke" and "thrombosis" and "cerebral hemorrhage" read on "a disease that is associated with "a blood vessel disorder, with the proviso that the blood disorder is not atherosclerosis." (see above rejection).

56. Houston et al (Tissue factor- a therapeutic target for thrombotic disorders, Expert Opinion in Therapeutic Targets, 2002. 6(2):159-174) teaches that thrombosis is the main cause of most cases of myocardial infarction and stroke (see page 159). Houston reviews the role of tissue factor in the development of both thrombosis and atherosclerosis, and ways to inhibit tissue factor to reduce the coagulation effects of TF (see pages 160-162). Houston teaches that statins have been shown to inhibit TF expression, and that the pleiotropic effects of statins are known to induce alterations in the coagulation pathway (page 163-165, table 1).

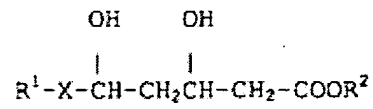
57. The administration of the pitavastatin would inherently cause an increase in expression of LKLF/KLF2. Furthermore, there is no teaching in the specification of how the mevalonic acid metabolic pathway inhibitors are different that those used in the prior art. In fact, in the examples 1-3 of the specification, applicant merely teaches the

incubation of HUVEC cells with known mevalonic acid inhibitors and measures KLF2 expression. The known inhibitors, known well before the date of filing of the instant application, inherently have the capability of increasing KLF2 expression.

58. It would have been obvious to the skilled artisan to combine the teachings of Patent application US 2005/0148626 on a method of administering a well known statin for treating a coagulation disorder, with the teaching of Houston et al on the leading cause of stroke is via thrombosis and the many beneficial effects of statins which make statins good candidates for anticoagulants, including those associated with blood vessel disorders, including thrombosis and stroke, and thus use known statins for treating alternate blood vessel disorders. Since the instant methodology relies upon the inherent effects of known compound, and the use of the compound to treat other diseases was known in the art, and thrombosis is associated with stroke and cerebral hemorrhage a skilled artisan would have a reasonable degree of success in practicing the claimed invention. All of the claimed elements were known in the prior art, and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention ((*See KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007)). *This is a provisional double patenting rejection.*

59. Claims 17-21, 25-28 and 33 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 11-17 of U.S.

Patent Publication No. US 2006/0257474 and Houston et al (Tissue factor- a therapeutic target for thrombotic disorders, Expert Opinion in Therapeutic Targets, 2002. 6(2):159-174) in view of Citak et al (Hemostatic problems and thromboembolic complications in nephrotic children. Pediatric Nephrology, 2000. 14:138-142). Although the conflicting claims are not identical, they are not patentably distinct from each other because Claims 17-21, 25-28 and 33 of the instant application represent a genus over the species claims 11-17 in U.S. Patent Publication No. US 2006/0257474. Instant claims 17-21, 25-28 and 33 read on a method for promoting expression of LKLF/KLF2 gene, which comprises administering to a subject in need thereof a mevalonic acid metabolic pathway inhibitor, wherein the subject suffers from a disease associated with a blood vessel disorder, with the proviso that the blood vessel disorder is not atherosclerosis, wherein the compound capable of inhibiting a mevalonic pathway, wherein the compound is represented by the formula (1):



wherein the compound comprises a variety of cyclic R groups and is limited to the lovastatin, pravastatin, simvastatin, fluvastatin, cerivastatin, atorvastatin, rosuvastatin, mevastatin, or pitavastin and the blood vessel disorder is cerebral hemorrhage. Broadly, these claims read on a method of inherently increasing LKLF expression by the administration of a mevalonic acid pathway inhibitor, including well known statins, to any subject in need thereof suffering from a blood disorder, with the proviso that the blood disorder is not atherosclerosis.

60. Claims 11-17 of U.S. Patent Publication No. US 2006/0257474 comprise a method of treating a glomerular disease comprising the administration to a patient of a therapeutic agent and pharmaceutical compositions comprising the HMG-CoA reductase inhibitor pitavastin. However, claims 11-17 of U.S. Patent Publication No. US 2006/0257474 do not recite a blood vessel disorder including cerebral hemorrhage.

61. The instant specification does not define "a disease associated with a blood vessel disorder" nor "cerebral hemorrhage."

62. Using the broadest reasonable interpretation, "stroke" and "thrombosis" and "cerebral hemorrhage" read on "a disease that is associated with "a blood vessel disorder, with the proviso that the blood disorder is not atherosclerosis." (see above rejection).

63. Houston et al (Tissue factor- a therapeutic target for thrombotic disorders, Expert Opinion in Therapeutic Targets, 2002. 6(2):159-174) teaches that thrombosis is the main cause of most cases of myocardial infarction and stroke (see page 159). Houston reviews the role of tissue factor in the development of both thrombosis and atherosclerosis, and ways to inhibit tissue factor to reduce the coagulation effects of TF (see pages 160-162). Houston teaches that statins have been shown to inhibit TF expression, and that the pleiotropic effects of statins are known to induce alterations in the coagulation pathway (page 163-165, table 1).

64. However, Houston does not teach the treatment of glomerular disease.

65. Citak et al (Hemostatic problems and thromboembolic complications in nephrotic children. Pediatric Nephrology, 2000. 14:138-142) teaches that thrombosis is a frequent risk and feature of the glomerular disease of nephortic syndrome (see page 159).

66. The administration of a statin, including pitavastatin would inherently cause an increase in expression of LKLF/KLF2. Furthermore, there is no teaching in the specification of how the mevalonic acid metabolic pathway inhibitors are different that those used in the prior art. In fact, in the examples 1-3 of the specification, applicant merely teaches the incubation of HUVEC cells with known mevalonic acid inhibitors and measures KLF2 expression. The known inhibitors, known well before the date of filing of the instant application, inherently have the capability of increasing KLF2 expression.

67. It would have been obvious to the skilled artisan to combine the teachings of Patent application US 2005/0148626 on a method of administering a well known statin for treating a coagulation disorder, with the teaching of Houston et al on the leading cause of stroke is via thrombosis and the many beneficial effects of statins make them good candidates for anticoagulants, including those associated with blood vessel disorders, including thrombosis, and stroke further with the teaching of Citak on the risk and association of glomerular diseases with thrombosis because the pleiotropic effects of statins were well known in the art and were already being used for treating diseases other than atherosclerosis. Since the instant methodology relies upon the inherent effects of known compound, and the use of the statin compound to treat other diseases was known in the art, and glomerular diseases is associated with thrombosis, stroke and cerebral hemorrhage a skilled artisan would have a reasonable degree of success in practicing the claimed invention. All of the claimed elements were known in the prior art, and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have

yielded predictable results to one of ordinary skill in the art at the time of the invention ((*See KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007)). *This is a provisional rejection.*

Claim Rejections - 35 USC § 112

68. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

69. Claims 17-20, 22-33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

70. Claim 17 (and dependent claims 18-20, 22-33) recites the limitation "the blood disorder" in 17. There is insufficient antecedent basis for this limitation in the claim.

71. There are very distinct differences between “blood disorders” and “blood vessel disorders”: one affects the actual vessel organ itself, whereas a “blood disorder” affects the blood within the vessel, not the vessel itself (i.e. sickle cell anemia, leukemia etc).

72. Claims 25-31 also recite the phrase “the blood disorder”. It is recommended that applicant amend this phrase to recite “blood vessel disorder" within these claims, as the ultimate antecedent basis for this phrase is indefinite.

Claim Rejections - 35 USC § 102

73. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

74. Claims 17-20, 25-28 and 32 are rejected under 35 U.S.C. 102(a) as being anticipated by Kawashima et al (HMG-CoA Reductase Inhibitor Has Protective Effects Against Stroke Events in Stroke Prone Spontaneously Hypertensive Rats. Stroke, 2000. 34:157-163 (published online December 5, 2002)). ***This rejection is necessitated by applicants amendments dated 10/05/07.***

75. Claims 17-20, 25-28 and 32 read on a method for promoting LKLF/KLF2 expression, which comprises administering to a subject suffering from a disease associated with a blood vessel disorder (with the proviso that the blood disorder is not atherosclerosis) an effective amount of a mevalonic acid pathway inhibitor, including well known statins (including cerivastatin) where the blood vessel disorder is cerebral hemorrhage. The substance is administered orally at a daily dosage of 0.01 to 1,000 mg.

76. Kawashima teaches the treatment of hypertensive rats with cerivastatin orally at 2mg/kg daily (see abstract and page 158). Kawashima reports that treatment with cerevastatin exerts a protective effect against stroke (see abstract, page 158) reduced cerebral damage, delayed the appearance of stroke associated symptoms and early death, increased eNOS expression, reduced superoxide production and decreases Stoke-associated infiltration of inflammatory cells (see pages 159-160). Kawashaima teaches that in spontaneously hypertensive rates, "stroke begins as very minor cerebral

lesions typically consisting of small pinpoint-sized hemorrhage" (page 161). Inherently, the application of cerevastatin would result in the increased expression of LKLF in the rats. Thus Kawashima teaches the claimed invention.

77. Claims 17-20, 25-28 and 32 are rejected under 35 U.S.C. 102(a) as being anticipated by Kishi et al (Atorvastatin causes depressor and sympatho-inhibitory effects with upregulation of nitric oxide synthases in stroke-prone spontaneously hypertensive rats. Journal of Hypertension, 2003. 21:379-386). ***This rejection is necessitated by applicants amendments dated 10/05/07.***

78. Claims 17-20, 25-28 and 32 read on a method for promoting LKLf/KLF2 gene, which comprises administering to a subject suffering from a disease associated with a blood vessel disorder (with the proviso that the blood vessel disorder is not atherosclerosis) an effective amount of a mevalonic acid pathway inhibitor, including well known statins including atorvastatin) where the blood vessel disorder is cerebral hemorrhage. The substance is administered orally at a daily dosage of 0.01 to 1,000 mg.

79. Kishi et al teaches the treatment of stroke prone hypertensive rats with atorvastatin results in a reduction of blood pressure through the increased production of eNOS and iNOS in the brain and aorta of the hypertensive rat (see abstract). The hypertensive rats were treated with atorvastatin orally at 50mg/kg daily (see abstract and page 380). Absent evidence to the contrary, the spontaneously hypertensive rats would have some degree of stroke, and Kishi et al teaches that the rates are stroke

prone, and inherently these strokes would be caused by cerebral hemorrhage (see Kawashaima et al above) Inherently, the application of atorvastatin would result in the increased expression of LKLF in the rats. Thus Kishi teaches the claimed invention.

80. Claims 17-20, 25-28 and 32 are rejected under 35 U.S.C. 102(b) as being anticipated by Amin-Hanjami et al (Mevastatin, an HMG-CoA Reductase Inhibitor, Reduces Stroke damage and Upregulated Endothelial Nitric Oxide Synthase in Mice. Stroke, 2001; 32:980-986). ***This rejection is necessitated by applicants amendments dated 10/05/07.***

81. Claims 17-20, 25-28 and 32 read on a method for promoting LKLf/KLF2 expression, which comprises administering to a subject suffering from a disease associated with a blood vessel disorder (with the proviso that the blood vessel disorder is not atherosclerosis) an effective amount of a mevalonic acid pathway inhibitor, including well known statins (including Mevastatin) where the blood vessel disorder is cerebral hemorrhage. The substance is administered orally at a daily dosage of 0.01 to 1,000 mg.

82. Amin-Hanjami et al teaches the treatment of mice with Mevastatin results in lower serum cholesterol and decreases the incidence of stroke and cardiovascular diseases, and increased expression of eNOS and cerebral blood flow resulting in neuroprotection in mice subjected to stroke (see abstract). The mice were treated with mevastatin parenterally at 2 or 20mg/kg daily (see abstract and page 981). Absent evidence to the contrary, the stroke model would have some degree of cerebral

hemorrhage. Inherently, the application of mevastatin would result in the increased expression of LKLF in the rats. Thus Amin-Hanjami teaches the claimed invention.

Claim Rejections - 35 USC § 103

83. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

84. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a). ***This rejection is necessitated by applicants amendments dated 10/05/07, or is modified from the previous office action to address new limitations in the claims.***

85. Claims 17-20, 22-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kishi et al (Atorvastatin causes depressor and sympatho-inhibitory effects with upregulation of nitric oxide synthases in stroke-prone spontaneously hypertensive rats. Journal of Hypertension, 2003. 21:379-386) and Hausding et al (Inhibition of small G

proteins of the Rho family by statins or Clostridium difficile toxin B enhances cytokine-mediated induction of NO synthase II. British Journal of Pharmacology, 2000.131:553-561) (of record) in view of Cohen et al (Inhibitors of Prenylation of Ras and Other G-proteins and Their Application as Therapeutics, Biochemical Pharacology,2000. 60:1061-1068). Claims 17-20, 22-32 read on a method for promoting LKLf/KLF2 expression, which comprises administering to a subject suffering from a disease associated with a blood vessel disorder (with the proviso that the blood vessel disorder is not atherosclerosis) an effective amount of a mevalonic acid pathway inhibitor, including well known statins, a farnesyltransferase inhibitor, a geranylgeranyltransferase I inhibitor, and a glucosyltransferase inhibitor, where the blood vessel disorder is cerebral hemorrhage and restenosis.

86. Kishi et al teaches the treatment of stroke prone hypertensive rats with atorvastatin results in a reduction of blood pressure through the increased production of eNOS (NOSIII) and iNOS (NOSII) in the brain and aorta of the hypertensive rat (see abstract). The hypertensive rats were treated with atorvastatin orally at 50mg/kg daily (see abstract and page 380). Absent evidence to the contrary, the spontaneously hypertensive rats would have some degree of stroke, and Kishi et al teaches that the rats are stroke prone, and inherently those strokes would be caused by cerebral hemorrhage (see Kawashaima et al above) Inherently, the application of atorvastatin would result in the increased expression of LKLF in the rats. Kishi does not teach the use of a farnesyltransferase inhibitor, a geranylgeranyltransferase I inhibitor, or a glucosyltransferase inhibitor.

87. Hausding et al teaches a method of investigating the Ras and or Rho pathway includes statins and Clostfidium difficile toxin B (TcdB) (a glucosyltransferase). He teaches that statins indirectly inhibit small G proteins by preventing their essential farnesylation (Ras) and/or geranylgeranlyation (Rho), wherein TcdB inactivates Rho-proteins directly (see abstract). He teaches that the use of the TcdB specifically inactivates the Rho proteins without affecting small G proteins of the Ras family (page 555, column II). Hausding teaches the use of statins lovastatin and atorvastatin and incubates the statins and the TcdB in human A549/8 and DLD-1 cells and murine NIH-3T3 cells (page 554). Hausding teaches that the cells are incubated with 3-100 uM of the statins, and .01 - 10 ng of Tcd - the incubations caused an increase in expression of NOS II mRNA, thereby being effective amounts.

88. Figure 1 of Hausding:

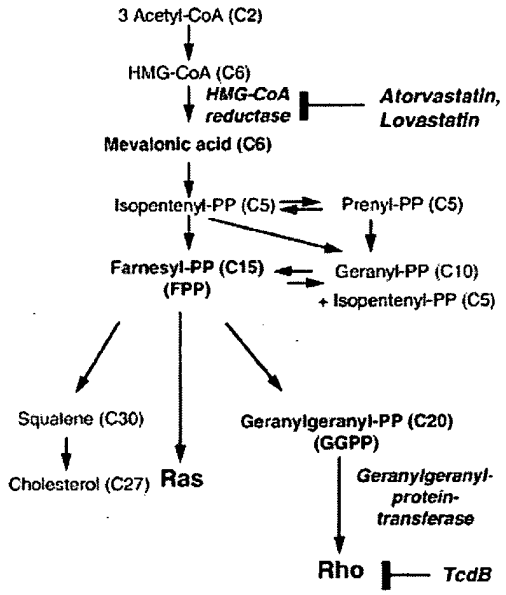


Figure 1 Biosynthesis of farnesylpyrophosphate and geranylgeranyl-pyrophosphate: effect of statins and toxin B from *Clostridium difficile*. Farnesylpyrophosphate (FPP) and geranylgeranylpyrophosphate (GGPP, synthesized from FPP by addition of a C5-moiety) are long lipophilic carbon chains that occur as intermediate products within the cholesterol biosynthesis pathway. Their formation depends on a sufficient supply of mevalonate by HMG-CoA reductase. Statins inhibit competitively this key enzyme of prenyl and cholesterol biosynthesis. Post-translational farnesylation or geranylgeranylation of small G proteins of the Ras/Rho family is an essential prerequisite for their anchoring in the cell membrane and thus for their activity. For Ras proteins farnesylation is the predominant mechanism, whereas Rho proteins are mainly geranylgeranylated. Toxin B from *Clostridium difficile* (TcdB) inactivates directly and specifically Rho proteins by UDP-glucosylation.

89.

90. Furthermore, there is no teaching in the specification of how the mevalonic acid metabolic pathway inhibitors are different than those used in the prior art. In fact, in the examples 1-3 of the specification, applicant merely teaches the incubation of HUVEC cells with known mevalonic acid inhibitors and measures KLF2 expression. The known inhibitors, known well before the date of filing of the instant application, including statins, farnesyltransferase inhibitors, geranylgeranyltransferase I inhibitors, and glucosyltransferase inhibitors inherently have the capability of increasing KLF2 expression, and fulfill the requirements of claims 1-4, 6-7, 9-12, 14-15,17-20, and 22-23 (see page 4 of the instant specification). However Hausding does not teach a method of

treating subject suffering with a disease associated with a blood vessel disorder, including restenosis.

91. Cohen et al (Inhibitors of Prenylation of Ras and Other G-proteins and Their Application as Therapeutics, Biochemical Pharacology,2000. 60:1061-1068) teaches that inhibitors of the mevalonic pathway are used to treat a variety of conditions including cancer, restenosis, angiogenesis and osteoporosis (see abstract and page 1062). He teaches the development of farnesyltransferase inhibitors (PFT) and geranylgeranyltransferase I inhibitors (PGGT-1) and that many of these inhibitors are able to function as both a PFT and a PGGT-1 inhibitor (see abstract). He teaches that "while protein prenylation is associated with cell growth, the potential of prenylation inhibitors as therapeutics in various diseases is obvious" and that restenosis after angioplasty (is post PTCA restenosis) results from the proliferation of smooth muscle cells in the vessel (page 1062). He further teaches that "It is conceivable that both farnysylation and geranylgeranylation must be suppressed to obtain effective inhibition of the proliferation of these cells. With this in mind, it may be sensible to develop inhibitors that are less discriminative between PFT and PGGT-1, such as the compounds described above" (page 1064). He further teaches that the use of the inhibitors is already being tested in clinical trials for cancer (ie administered to a subject in need thereof), but that the testing for other diseases is eminent (page 1066).

92. Figure 1 of

Cohen:

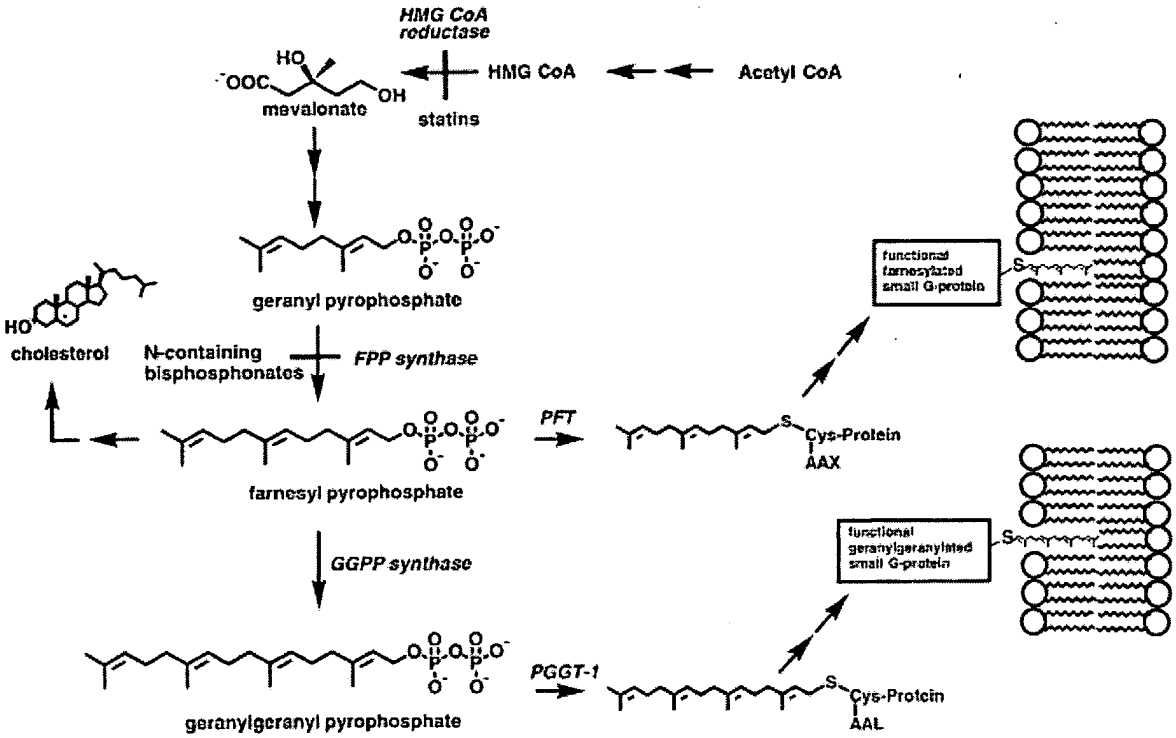


FIG. 1. Biosynthesis pathway of isoprenoids leading to prenylated proteins. Statins are specific inhibitors of HMG-CoA reductase (the rate-limiting enzyme of cholesterol biosynthesis) and NCBPs of the enzyme FPP synthase. The chemical structures of the prenyl groups are shown and the positions of the protein prenylating enzymes PFT and PGGT-1 are indicated. After prenylation, the proteins are further modified and will finally move to the cellular membranes where they exert their signalling function.

It would have been obvious to the skilled artisan to combine the teachings of Kishi on a method for promoting LKLf/KLF2 expression, which comprises administering to a subject suffering from a disease associated with a blood vessel disorder (with the proviso that the blood vessel disorder is not atherosclerosis) an effective amount of a mevalonic acid pathway inhibitor, including well known statins further through the upregulation of eNOS and iNOS with the teaching of Hausding on the beneficial effect of using additional inhibitor of the mevalonic pathway including statins lovastatin and

atorvastatin and the glucosyltransferase TcdB in human A549/8 and DLD-1 cells and murine NIH- 3T3 cells capable of increasing in expression of NOS II mRNA (iNOS), further with the teaching of Cohen that inhibitors of the mevalonic pathway are targets for the design of clinical therapeutics on a variety of diseases, including statins, and farnesyltransferase inhibitors (PFT) and geranylgeranyltransferase I inhibitors (PGGT-1), and that many of these inhibitors are able to function as both a PFT and a PGGT-1 inhibitor because both Kishi and Hausding teach the beneficial upregulation of NOS in response to the application of mevalonic pathway inhibitors in reducing stroke and cerebral hemorrhage damage by reducing blood pressure, and Cohen points to the application of the therapeutic potential to treat blood vessel disorders, including restenosis using said inhibitors. The instant application teaches that an inherent property of the application of the statins, the farnesyltransferase inhibitors (PFT) and geranylgeranyltransferase I inhibitors glucosyltransferase TcdB is the upregulation of LKLF (see page 4). All of the claimed elements were known in the prior art, and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention ((See *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007)). Given the teachings of the prior art and the level of skill of the ordinary skilled artisan at the time the instant invention was made, it must be considered that said ordinary skilled artisan would have had reasonable expectation of success in practicing the claimed invention.

93. Claim 33 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kishi et al (Atorvastatin causes depressor and sympatho-inhibitory effects with upregulation of nitric oxide synthases in stroke-prone spontaneously hypertensive rats. Journal of Hypertension, 2003. 21:379-386) as applied to claim 17 above, and further in view of Kajinami et al (NK-104: a novel synthetic HMG-CoA reductase inhibitor. Expert Opinion on Investigational Drugs, 2000. 9(11)2653-2661.). Claim 33 reads on a method for promoting expression of LKLF gene, which comprises administering to a subject in need thereof suffering from a blood vessel disorder (that is not atherosclerosis) a mevalonic pathway inhibitor capable to promoting expression of LKLF, wherein the substance is pitavastatin.

94. Kishi et al teaches a method for promoting expression of LKLF, which comprises administering to a subject in need thereof suffering from a blood vessel disorder (that is not atherosclerosis) a mevalonic pathway inhibitor capable to promoting expression of LKLF. Kishi teaches this method by administering the statin Atorvastatin. Kishi does not teach the use of Pitavastatin.

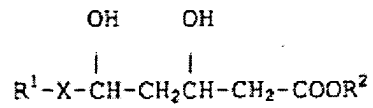
95. Kajinami teaches the development of NK-104 (also known as pitavastatin), that "is dose-dependent and appears to be equivalent to that of atorvastatin. This new statin is safe and well tolerated in the treatment of patients with hypercholesterolaemia. The cytochrome P450 system only slightly modifies NK-104, which suggests the clinical advantage of this agent, because the prevalent of clinically significant interaction with a number of other commonly used drugs can be considered to be extremely low. NK-104

can provide a new and potentially superior therapeutic agent when compared with currently available other statins" (see abstract).

96. It would have been obvious to the skilled artisan to combine the teachings of Kishi on a method for promoting expression of LKLF expression, which comprises administering to a subject in need thereof suffering from a blood vessel disorder (that is not atherosclerosis) a mevalonic pathway inhibitor capable of inherently promoting expression of LKLF using atorvastatin with the teaching of Kajinami et al on the development of a new statin that has the same effectiveness as atorvastatin, but fewer drug interactions because the patient being treated would be less susceptible to adverse side effects from multiple medications. All of the claimed elements were known in the prior art, and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention ((See *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007)). Given the teachings of the prior art and the level of skill of the ordinary skilled artisan at the time the instant invention was made, it must be considered that said ordinary skilled artisan would have had reasonable expectation of success in practicing the claimed invention.

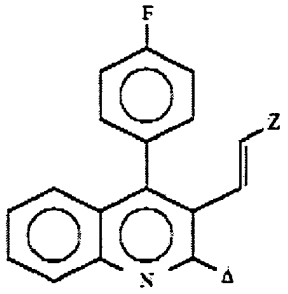
97. Claims 17-20, 25-28 and 33 are rejected under 35 U.S.C. 103(a) as being obvious over Fujikawa et al (U.S. Patent No. 5,856,336) in view of Gertz et al (Withdrawal of Statin Treatment Abrogates Stroke Protection in Mice, Stroke, 2003. 34:551-557). Instant claims 17-20, 25-28 and 33 read on a method for promoting

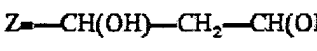
expression of LKLF/KLF2, which comprises administering to a subject in need thereof a mevalonic acid metabolic pathway inhibitor, wherein the subject suffers from a diseases associated with a blood vessel disorder, with the proviso that the blood disorder is not atherosclerosis, wherein the compound capable of inhibiting a mevalonic pathway, wherein the compound is represented by the formula (1):



wherein the compound comprises a variety of cyclic R groups and is limited to the lovastatin, pravastatin, simvastatin, fluvastatin, cerivastatin, atorvastatin, rosuvastatin, mevastatin, or pitavastin and the blood vessel disorder is cerebral hemorrhage. Broadly, these claims read on a method of inherently increasing LKLF expression by the administration of a mevalonic acid pathway inhibitor, including well known statins, to any subject in need thereof, with the proviso that the blood disorder is not atherosclerosis. Broadly, these claims read on a method of inherently increasing LKLF expression by the administration of a mevalonic acid pathway inhibitor, including well known statins, to any subject in need thereof, with the proviso that the blood disorder is not atherosclerosis.

98. Patent 5,856,336 discloses the chemical structure for pitavastatin in claim 1:



99.  , and the methods for the use of pitavastatin in claim 2, specifically, "A method for reducing hyperlipidemia, hyperlipoproteinemia or atherosclerosis, which comprises administering an effective amount of the compound of formula A as defined in claim 1." The structure of the molecule of patent 5,856,336 inherently embodies the structural limitations of the instant methods claims. However, Patent 5,856,336 is limited to treating atherosclerosis, or hyperlipidemia or hyperlipoproteinemia", not a blood vessel disorder, including cerebral hemorrhage.

100. The instant specification does not define "a disease associated with a blood vessel disorder" nor "cerebral hemorrhage."

101. The Colombia Encyclopedia, 2004 teaches the definition of stroke:

102. Destruction of brain tissue as a result of intracerebral hemorrhage or infarction caused by thrombosis (clotting) or embolus (obstruction in a blood vessel caused by clotted blood or other foreign matter circulating in the bloodstream); formerly called apoplexy. Cerebral hemorrhage or thrombosis occurs most often in elderly persons with constricted arteries (see arteriosclerosis), although either may also be caused by inflammatory or toxic damage to the cerebral blood vessels. Cerebral embolism may occur at any age, even in children.

103. Symptoms of stroke develop suddenly. In cases of severe brain damage there may be deep coma, paralysis of one side of the body, and loss of speech, followed by death or permanent neurological disturbances after recovery. If the brain damage sustained has been slight, there is usually complete recovery, but most survivors of

stroke require extensive rehabilitation. Hypertension, which is a major cause of intracranial hemorrhage and stroke, can be treated by preventive measures using diet (e.g., increasing nutrients such as antioxidants and folate), drug therapy, and stress reduction techniques. Other preventive measures for people at high risk include daily aspirin to retard clot formation and surgical correction of the narrowed carotid artery. Sometimes surgical removal of the clot is possible on larger vessels, but it is usually pointless after the stroke or when blockage is widespread. The thrombolytic drug tissue plasminogen activator, widely used to treat heart attacks, has been approved for use within three hours of the onset of strokes caused by clots.

104. Using the broadest reasonable interpretation, "stroke" and "thrombosis" and "cerebral hemorrhage" read on "a disease that is associated with "a blood vessel disorder, with the proviso that the blood disorder is not atherosclerosis."

105. Gertz et al (Withdrawal of Statin Treatment Abrogates Stroke Protection in Mice, Stroke, 2003. 34:551-557) teaches that the use of statins, including atorvastatin provides neuronal protection and reduces thrombus formation in mice, independent of lipid lowering in mice (see abstract) Gertz teaches that statins have many pleotropic effects, other than mevalonic acid pathway inhibitors, including, reducing myocardial infarct size and stroke possibly through direct effects on endothelium with antithrombotic and anti-inflammatory effects, that statins have been shown to upregulate eNOS in vasculature and thrombocytes, decrease platelet activation, augment cerebral blood flow, and protect from cerebral ischemia in wild-type mice (see page 551).

106. The administration of the pitavastatin would inherently cause an increase in expression of LKLF/KLF2. Furthermore, there is no teaching in the specification of how the mevalonic acid metabolic pathway inhibitors are different that those used in the prior art. In fact, in the examples 1-3 of the specification, applicant merely teaches the incubation of HUVEC cells with known mevalonic acid inhibitors and measures KLF2

expression. The known inhibitors, known well before the date of filing of the instant application, inherently have the capability of increasing KLF2 expression.

107. It would have been obvious to the skilled artisan to combine the teachings of Patent No. 5,856,336 on a method of administering a well known statin for treating atherosclerosis, hyperlipidemia or hyperlipoproteinemia, with the teaching of Gertz et al on the many pleiotropic effects of statins that make statins good candidates for treating other diseases, including those associated with blood disorder, including thrombosis, cerebral hemorrhage and stroke. Since the instant methodology relies upon the inherent effects of known compounds, and the use of the compound to treat other diseases was known in the art, a skilled artisan would have a reasonable degree of success in practicing the claimed invention. All of the claimed elements were known in the prior art, and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention ((*See KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007)).

108. The applied reference has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(b). This rejection under 35 U.S.C. 102(b) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

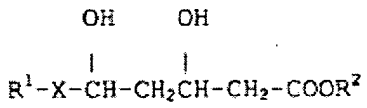
109. Claims 17-20, 25-28 and 33 are directed to an invention not patentably distinct from claims 1-2 of commonly assigned US Patent No. 5,856,336. Specifically, instant claims 17-20, 25-28 and 33 are a genus of the species claims in US Patent No. 5,856,336, and are therefor encompassed by the subject matter in claims of US Patent No. 5,856,336.

110. The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300). Commonly assigned US Patent No. 5,856,336, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

111. A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

112. Claims 17-20, 25-28 and 33 are rejected under 35 U.S.C. 103(a) as being obvious over Morikawa et al (US Patent Publication No. US 2003/0195167) and Gertz et al (Withdrawal of Statin Treatment Abrogates Stroke Protection in Mice, Stroke, 2003.

34:551-557) in view of Meroni et al (Anti-Inflammatory and Immunomodulating Properties of Statins, Clinical Reviews in Allergy and Immunology, 2002. 23:263-277). Claims 17-20, 25-28 and 33 read on a method for promoting expression of LKLF/KLF2, which comprises administering to a subject in need thereof a mevalonic acid metabolic pathway inhibitor, wherein the subject suffers from a diseases associated with a blood vessel disorder, with the proviso that the blood disorder is not atherosclerosis, wherein the compound capable of inhibiting a mevalonic pathway, wherein the compound is represented by the formula (1):



wherein the compound comprises a variety of cyclic R groups and is limited to the lovastatin, pravastatin, simvastatin, fluvastatin, cerivastatin, atorvastatin, rosuvastatin, mevastatin, or pitavastin and the blood vessel disorder is cerebral hemorrhage. Broadly, these claims read on a method of inherently increasing LKLF expression by the administration of a mevalonic acid pathway inhibitor, including well known statins, to any subject in need thereof, with the proviso that the blood disorder is not atherosclerosis.

113. Morikawa et al (US Patent Publication No. 2003/0195167) teaches a method of suppressing expression of the PTX3 genes using pitavastatin, method of treating autoimmune disease and rheumatoid arthritis using pitavasatin (see claims 1-15).

114. Furthermore, there is no teaching in the specification of how the mevalonic acid metabolic pathway HMG-CoA reductase inhibitor pitavastatin is different than that used in the prior art. In fact, in the examples 1-3 of the specification, applicant merely teaches

the incubation of HUVEC cells with known mevalonic acid inhibitors and measures KLF2 expression. The known inhibitors, known well before the date of filing of the instant application, inherently have the capability of increasing KLF2 expression, and fulfill the requirements of claims 9-13, 17-21. However, Morikawa does not teaches administering the statin to a patient with a blood vessel disorder as described in the instant claims.

115. Gertz et al (Withdrawal of Statin Treatment Abrogates Stroke Protection in Mice, Stroke, 2003. 34:551-557) teaches that the use of statins, including atorvastatin provides neuronal protection and reduces thrombus formation in mice, independent of lipid lowering in mice (see abstract) Gertz teaches that statins have many pleiotropic effects, other than mevalonic acid pathway inhibitors, including, reducing myocardial infarct size and stroke possibly through direct effects on endothelium with antithrombotic and anti-inflammatory effects, that statins have been shown to upregulate eNOS in vasculature and thrombocytes, decrease platelet activation, augment cerebral blood flow, and protect from cerebral ischemia in wild-type mice (see page 551).

116. Meroni et al (Anti-Inflammatory and Immunomodulating Properties of Statins, Clinical Reviews in Allergy and Immunology, 2002. 23:263-277). Meroni teaches that "since the modern view defines atherosclerosis as a chronic inflammatory disorder, it has been suggested that systemic inflammation and soluble immune mediators (circulating autoantibodies, immune-complexes, complement activation products) might play a role in accelerating vessel pathology. The main target appears to be the endothelium because of its ability to switch to a pro-adhesive, pro-inflammatory and pro-

coagulant surface in response to theses mediators" (page 263). Recent advances in the knowledge of the pharmacology of statins have indicated that these drugs (rather than to solely be simple cholesterol lowering molecules) display multiple pleiotropic effects on several cellular mechanisms involved in the atherosclerotic plaque formation. Their anti-inflammatory activity and particularly their ability to down regulate endothelial cell activation and induced by different stimuli strongly suggest their possible use in conditions in which the systemic inflammation and the endothelial activation/damage are thought to represent key pathogenic mechanisms" (page 264).

117. It would have been obvious to the skilled artisan to combine the teachings of US Patent Publication No. 2003/0195167on a method of administering a well known statin for treating autoinflammatory diseases, with the teaching of Gertz et al on the many pleiotropic effects of statins that make statins good candidates for treating other diseases, including those associated with blood disorder, including thrombosis, cerebral hemorrhage and stroke due to statins anti-thrombotic, anti-apoptotic and anti-inflammatory effects further with the teaching of Meroni on the potential therapeutic use of statins for treating autoimmune inflammatory diseases with statins, because the therapeutic potential to treat a number of different diseases with well known inhibitors would broaden the use of known compounds. Since the instant methodology relies upon the inherent effects of known compound, and the use of the compound to treat other diseases was known in the art, a skilled artisan would have a reasonable degree of success in practicing the claimed invention. All of the claimed elements were known in the prior art, and one skilled in the art could have combined the elements as claimed

by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention ((*See KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007)).

118. The applied reference has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Response to Arguments

119. Applicant's arguments filed 10/05/07 have been fully considered but they are not fully persuasive.

Response to double patenting rejections:

120. Claims 1-5, 9-13 and 17-21 were rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 2 of U.S. Patent No. 5,856,336. Applicants argue that the patent 5,856,336 is not directed to a method of administering to a subject suffering from a blood vessel disorder, and therefore should be withdrawn.

121. The examiner is respectfully not persuaded. While the examiner acknowledges that the 5,856,336 patent is not directed to treating the specific disorders listed in the instant claims, at the time of the invention, the pleiotropic effects of statins were well known and were being used to treating other maladies (see Gertz). Additionally, the

instant claims are directed to the modulation of the LKLF gene solely through the administration of the agent: this is an inherent property of the compound, and thus the modulation of LKLF would inherently occur. Thus it would have been obvious for the skilled artisan to modify the claims of the 5,856,336 patent to treat alternate blood vessels disorders, such as those listed in the instant claims.

122. Claims 1-5, 9-13 and 17-21 were rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-5 of U.S. Patent No. 5,872,130. Applicants argue that the patent 5,872,130 is not directed to a method of administering to a subject suffering from a blood vessel disorder, and therefore should be withdrawn.

123. The examiner is respectfully not persuaded. While the examiner acknowledges that the 5,872,130 patent is not directed to treating the specific disorders listed in the instant claims, at the time of the invention, the pleiotropic effects of statins were well known and were being used to treating other maladies (see Gertz). Additionally, the instant claims are directed to the modulation of the LKLF gene solely through the administration of the agent: this is an inherent property of the compound, and thus the modulation of LKLF would inherently occur. Thus it would have been obvious for the skilled artisan to modify the claims of the 5,872,130 patent to treat alternate blood vessels disorders, such as those listed in the instant claims.

124. Claims 9-13 and 17-21 were rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-2 of U.S. Patent No. 7,022,713. Applicants argue that the patent 7,022,713 is not directed to a method of administering to a subject suffering from a blood vessel disorder, and therefore should be withdrawn.

125. The examiner is respectfully not persuaded. While the examiner acknowledges that the 7,022,713 patent is not directed to treating the specific disorders listed in the instant claims, at the time of the invention, the pleiotropic effects of statins were well known and were being used to treating other maladies (see Gertz). Additionally, the instant claims are directed to the modulation of the LKLF gene solely through the administration of the agent: this is an inherent property of the compound, and thus the modulation of LKLF would inherently occur. Thus it would have been obvious for the skilled artisan to modify the claims of the 7,022,713 patent to treat alternate blood vessels disorders, such as those listed in the instant claims.

126. Claims 1-5, 9-13 and 17-21 were rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-2 and 7-13 of U.S. Patent Publication No. US 2005/0148626. Applicants argue that the patent 7,022,713 is not directed to a method of administering to a subject suffering from a blood vessel disorder, and therefore should be withdrawn.

127. The examiner is respectfully not persuaded. While the examiner acknowledges that the US 2005/0148626 patent application is not directed to treating the specific disorders listed in the instant claims, at the time of the invention, the pleiotropic effects

of statins was well known and were being used to treating other maladies (see Houston). Additionally, the instant claims are directed to the modulation of the LKLF gene solely through the administration of the agent: this is an inherent property of the compound, and thus the modulation of LKLF would inherently occur. Thus it would have been obvious for the skilled artisan to modify the claims of the US 2005/0148626 patent application to treat alternate blood vessels disorders, such as those listed in the instant claims.

128. Claims 9-13 and 17-21 were rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-17 of U.S. Patent Publication No. US 2006/0217352. The examiner is assuming applicants are arguing that the Patent Publication No. US 2006/0217352 is not directed to a method of administering to a subject suffering from a blood vessel disorder, and therefore should be withdrawn. However, Applicant's specific arguments against this rejection are actually directed to US 2005/0148626 NOT US 2006/0217352 (see page 15 of applicant's response).

129. The examiner is respectfully not persuaded. While the examiner acknowledges that the Patent Publication No. US 2006/0217352 is not directed to treating the specific disorders listed in the instant claims, at the time of the invention, the pleiotropic effects of statins were well known and were being used to treating other maladies (see Houston). Additionally, the instant claims are directed to the modulation of the LKLF gene solely through the administration of the agent: this is an inherent property of the compound, and thus the modulation of LKLF would inherently occur. Thus it would

have been obvious for the skilled artisan to modify the claims of the US 2006/0217352 patent application to treat alternate blood vessels disorders, such as those listed in the instant claims.

130. Claims 1-5, 9-13 and 17-21 were rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7 and 9-17 of U.S. Patent Publication No. US 2006/0257474. Applicants argue that the patent 7,022,713 is not directed to a method of administering to a subject suffering from a blood vessel disorder, and therefore should be withdrawn.

131. The examiner is respectfully not persuaded. While the examiner acknowledges that the US 2006/0257474 patent application is not directed to treating the specific disorders listed in the instant claims, at the time of the invention, the pleiotropic effects of statins were well known and were being used to treating other maladies (see Houston and Citak). Additionally, the instant claims are directed to the modulation of the LKLF gene solely through the administration of the agent: this is an inherent property of the compound, and thus the modulation of LKLF would inherently occur. Thus it would have been obvious for the skilled artisan to modify the claims of the US 2006/0257474 patent application to treat alternate blood vessels disorders, such as those listed in the instant claims.

132. Additionally, applicants argue that the previous office action rejections claims 1-5, 9-13 and 17-21 on obvious-type double patenting (application 10/504,851) and a withdrawal of this rejection in light of the abandonment of the 10/504851 application.

This rejection was not made in the previous office action, thus there is no rejection to be withdrawn.

Response to 112 2nd rejections

133. Applicant's arguments, with respect to rejections of claims 2, 9 and 18 as being indefinite for the phrase "lactone derivative" have been fully considered and are persuasive. The 112 2nd rejection of claims 2, 9 and 18 has been withdrawn.

Response to 102 rejections

134. Claims 9-13,17-21 were rejected under 35 U.S.C. 102(b/e) as being anticipated by Morikawa et al (US Patent Publication No. US 2003/0195167). Applicants traverse this rejection and argue that Morikawa does not teach administering mevalonic acid pathway inhibits to a subject suffering from blood vessel disorders as listed in the claims.

135. The examiner is respectfully not persuaded. While the examiner acknowledges that the US 2003/0195167 patent application is not directed to treating the specific disorders listed in the instant claims, at the time of the invention, the pleiotropic effects of statins were well known and were being used to treating other maladies (see Gertz et al and Meroni et al). Additionally, the instant claims are directed to the modulation of the LKLF gene solely through the administration of the agent: this is an inherent property of the compound, and thus the modulation of LKLF would inherently occur. Thus it would have been obvious for the skilled artisan to modify the claims of the Morikawa to treat alternate blood vessels disorders, such as those listed in the instant claims.

136. Applicants have not provided any arguments against the rejection of claims 1-5, 9-13, 17-21 under 35 U.S.C. 102(b/e) as being anticipated by Fujikawa et al (US Patent No. 5,856,336). It appears that applicants have mixed up references, and provided arguments against Fujikawa US patent 5,854,259 inadvertently. In this traversal, applicant argues that Fujikawa does not teach administering mevalonic acid pathway inhibits to a subject suffering from blood vessel disorders as listed in the claims (page 10 bridging to 11).

137. The examiner is respectfully not persuaded. While the examiner acknowledges that the 5,856,336 patent is not directed to treating the specific disorders listed in the instant claims, at the time of the invention, the pleiotropic effects of statins was well known and were being used to treating other maladies (see Gertz). Additionally, the instant claims are directed to the modulation of the LKLF gene solely through the administration of the agent: this is an inherent property of the compound, and thus the modulation of LKLF would inherently occur. Thus it would have been obvious for the skilled artisan to modify the claims of the Fujikawa to treat alternate blood vessels disorders, such as those listed in the instant claims.

138. Claims 1-4, 8-12, 16-20 and 24 were rejected under 35 U.S.C. 102(b/e) as being anticipated by Hausding et al. Applicants traverse this rejection and argue that Hausding does not teach administering mevalonic acid pathway inhibits to a subject suffering from blood vessel disorders as listed in the claims.

139. The examiner is respectfully not persuaded. While the examiner acknowledges that Hausding is not directed to treating the specific disorders listed in the instant claims, at the time of the invention, the pleiotropic effects of statins were well known and were being used to treating other maladies (see Kishi, and Cohen above). Additionally, the instant claims are directed to the modulation of the LKLF gene solely through the administration of the agent: this is an inherent property of the compound, and thus the modulation of LKLF would inherently occur. Thus it would have been obvious for the skilled artisan to modify the teaching of Hausding to treat alternate blood vessels disorders, such as those listed in the instant claims.

140. Claims 9-13 and 17-21 were rejected under 35 U.S.C. 102(b/e) as being anticipated by Lerner et al. In light of applicant's arguments, this rejection is withdrawn. The examiner aggress that Lerner does not suggestion that the inhibitors can be administer to a subject having blood vessel disorders as claimed.

Conclusion

141. No claims are allowed. As demonstrated above the multiple pleotrophic effects of statins were well known at the time of the invention and were subjected to treating or attempting to treat a myriad of diseases. The mevalonic pathway was an obvious target for treating these diseases and often times an inhibitor was capable of inhibiting multiple points along the pathway. Additionally the LKLF modulatory capabilities ascribed to the inhibitors by applicant are an inherent capability according to applicant (see page 4 of the instant specification).

142. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly A. Makar, Ph.D. whose telephone number is 571-272-4139. The examiner can normally be reached on 8AM - 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D. can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Kam/01/09/08

DAVID GUZO
PRIMARY EXAMINER